

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:  
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**PCT**

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## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

<p>To: PAMELA J. SHERWOOD BOZICEVIC, FIELD &amp; FRANCIS LLP 1900 UNIVERSITY AVENUE, SUITE 200 EAST PALO ALTO, CA 94303</p>		<p><b>04 NOV 2005</b></p>
<p>Date of mailing (day/month/year)</p>		<p><b>04 NOV 2005</b></p>
<p>Applicant's or agent's file reference</p>		<p><b>FOR FURTHER ACTION</b> See paragraph 2 below</p>
<p>STAN-324WO</p>		
<p>International application No.</p>	<p>International filing date (day/month/year)</p>	<p>Priority date (day/month/year)</p>
<p>PCT/US04/37692</p>	<p>09 November 2004 (09.11.2004)</p>	<p>10 November 2003 (10.11.2003)</p>
<p>International Patent Classification (IPC) or both national classification and IPC</p>		
<p>IPC(7): C12Q 1/68; G01N 33/53; C12N 9/00; A61K 48/00; A01N 37/18; A61K 48/00; C07K 14/00; A01K 67/00 and US Cl.: 435/6, 7.1, 183; 514/2, 44; 530/350; 800/8</p>		
<p>Applicant</p>		
<p>THE BOARD OF TRUSTEES OF STANFORD UNIVERSITY</p>		

**1. This opinion contains indications relating to the following items:**

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

**3. For further details, see notes to Form PCT/ISA/220.**

<p>Name and mailing address of the ISA/ US</p> <p>Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230</p>	<p>Date of completion of this opinion</p> <p>06 October 2005 (06.10.2005)</p>	<p>Authorized officer</p> <p>Mark L. Shibuya <i>[Signature]</i> Telephone No. (571) 272-1600 <i>[Signature]</i></p>
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Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International

PCT/US04/37692

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed  
☐ a translation of the international application into \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing  
☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper  
☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.  
☐ filed together with the international application in electronic form.  
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE  
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International PCT/US04/37492

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1-19, 22-24</u>	YES
	Claims <u>20, 21</u>	NO
Inventive step (IS)	Claims <u>1-19, 22-24</u>	YES
	Claims <u>20, 21</u>	NO
Industrial applicability (IA)	Claims <u>1-24</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 20 and 21 lack novelty under PCT Article 33(2) as being anticipated by BALAKIREV, M.Y. et al., EMBO Reports, April 2003, Vol. 4, No. 5, pages 517-522.

BALAKIREV, M.Y. et al., throughout the publication, teach otubains that would inherently be capable of stabilizing or destabilizing GRAIL.

Claims 1-19 and 22-24 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest methods comprising GRAI, otubain isoforms and USP8 and ras-GRF1, methods of determining substrates of an E3 ligase comprising introducing into cells a library of vectors comprising sequences fused to candidate E3 ligase substrate coding sequences, animal models for biological function of the GRAIL complex, methods of treating a proliferative disorder comprising administering a therapeutic amount of a biologically active agent that modulates the activity of the GRAIL complex, an isolated polypeptide complex comprising GRAIL and one or more of a otubain isoform and USP8 and ras-GRF1, and a method of diagnosing a defect in immune tolerance or cellular proliferation by determining the level of an otubain isoform polypeptide.

Claims 1-24 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry.